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The Effect of the Inner-Hair-Cell Mediated Transduction on the Shape of Neural Tuning Curves

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Abstract. The inner hair cells of the mammalian cochlea transform the vibrations of their stereocilia into releases of neurotransmitter at the ribbon synapses, thereby controlling the activity of the afferent auditory fibers. The mechanical-to-neural transduction is a highly nonlinear process and it introduces differences between the frequency-tuning of the stereocilia and that of the afferent fibers. Using a computational model of the inner hair cell that is based on *in vitro* data, we estimated that smaller vibrations of the stereocilia are necessary to drive the afferent fibers above threshold at low (≤0.5 kHz) than at high (≥4 kHz) driving frequencies. In the base of the cochlea, the transduction process affects the low-frequency tails of neural tuning curves. In particular, it introduces differences between the frequency-tuning of the stereocilia and that of the auditory fibers resembling those between basilar membrane velocity and auditory fibers tuning curves in the chinchilla base. For units with a characteristic frequency between 1 and 4 kHz, the transduction process yields shallower neural than stereocilia tuning curves as the characteristic frequency decreases. This study proposes that transduction contributes to the progressive broadening of neural tuning curves from the base to the apex.

INTRODUCTION

The inner hair cells (IHCs) transduce the vibration of the organ of Corti into releases of neurotransmitter at their synapses through a chain of electromechanical processes; the release of neurotransmitter at the IHC synapse evoke action potentials in the afferent auditory fiber (AF). These transformations introduce various linear and nonlinear distortions, which create a frequency dependent relationship between the amplitude of the stereocilia vibrations and the average discharge rate of the afferent AFs. In particular, we concluded that smaller stereocilia vibrations are necessary to drive the AFs above threshold at low rather than at high frequencies [1]. Consequently, the AFs enhanced sensitivity to low-frequency vibrations of the cilia causes the frequency-tuning of the AFs to be different than that of the IHC stereocilia. In this study we show (qualitatively rather than quantitatively) how transduction affects the shape of neural tuning curves relative to constant stereocilia deflection contours, and how this process depends on the characteristic frequency (CF) of the considered AF.

The Frequency Sensitivity of Transduction

In our previous study [1], we investigated the frequency-dependent relationship between mean-rate thresholds of the AFs and vibrations of the stereocilia in the mammalian base, using the model presented in Fig. 1A. Briefly, the model includes a description of the most prominent IHC membrane currents based on *in vitro* measurements from mature gerbil IHCs [5, 7]. The model incorporates the kinetics of the voltage-gated whole-cell Ca^{2+} current, which drives a simplified model of exocytosis through a quasi-linear synaptic transfer function. This quasi-linear function might be interpreted as the first-order polynomial expansion of a nonlinear function relating whole-cell Ca^{2+} current and exocytosis rate. Although the empirical relationship between Ca^{2+} current and exocytosis rate in high-frequency IHCs is approximately linear [4, 8], a nonlinear relationship between whole-cell Ca^{2+} current and exocytosis rate at a particular synapse is expected because the gating of Ca^{2+} channels shows large variability across synapses [10]. Finally, we assume that near threshold the effects of synaptic depression and AF refractoriness can be considered

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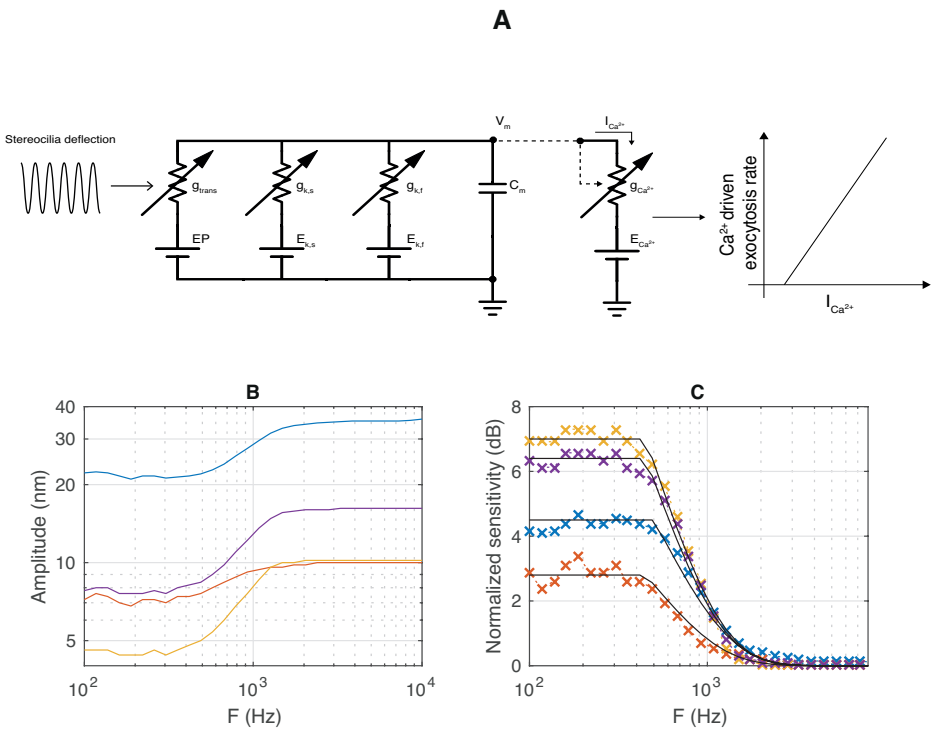

FIGURE 1. A) Model of mechanical to neural transduction employed to estimate the frequency sensitivity of the IHC-mediated transduction process. B) Stereocilia deflection amplitude corresponding to threshold levels for different auditory fiber models (different spontaneous and saturation discharge rates) as a function of the stereocilia oscillation frequency. C) Synaptic frequency sensitivity, obtained by normalizing and reciprocating the curves in B). Open symbols: simulated data points; continuous lines: fits using Eq. (1).

small and thus we assume that the discharge rate of the AF approximately reflects the exocytosis rate at the synapse. The parameters of the synaptic transfer function were varied to generously match the range of spontaneous and peak AF discharge rates reported in various animal studies.

With this model, we computed the amplitude of the stereocilia oscillation corresponding to AF threshold for different frequencies and for a large variety of model parameters. An example of the stereocilia oscillation amplitude corresponding to AF threshold for four AF models is presented in Fig. 1B. The same curves are normalized and reciprocated in Fig. 1C. The curves in Fig. 1C represent the sensitivity of the AFs to the frequency of the stereocilia oscillation, and we refer to this metric as *synaptic frequency sensitivity*. We further assessed the robustness of the estimations by letting the free parameters of the model to assume a wide range of parameters and by systematically altering the model parameters based on measurements. We concluded that the synaptic-frequency sensitivity ($S(f)$) is meaningfully approximated by:

$$S(f) = \begin{cases} P, & f < f_c \\ Pe^{\frac{f_c - f}{f_c}}, & f \geq f_c \end{cases} \tag{1}$$

where f_c is the cut-off frequency corresponding to the IHC membrane time-constant, and P a value that depends mostly on the parameters controlling the synaptic-transfer function and the activation of the mechano-electrical transduction (MET) channels. Because of the heterogeneity of Ca^{2+} signaling across synapses of the same IHC [10], we concluded that P is subject to substantial variability *in vivo*. We estimated f_c = 500 Hz and P spanning from about 2 to 9 dB in the base of the gerbil, with a median value of 5 dB over 200 simulations [1].

The transduction machinery differs in basal and apical units. In particular, apical IHCs have a higher cut-off frequency than basal units due to the significant presence of a linotop-sensitive K^+ current ($I_{K,n}$, [6]). Furthermore, in the apex the relationship between whole-cell Ca^{2+} current and whole-cell exocytosis rate is best captured by a cubic function [8]. A higher IHC cut-off frequency in apical than in basal unit is consistent with the chinchilla data showing a higher phase-locking limit for AFs with a low-CF [14]. Unfortunately, species differences, limited *in vitro* data as

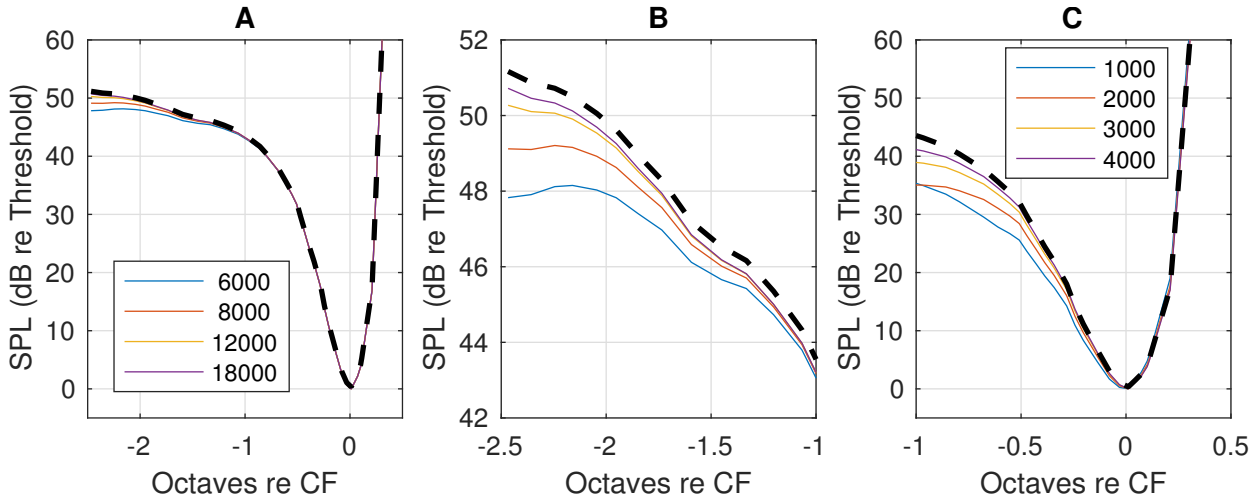

FIGURE 2. Estimated neural tuning curves from an hypothetical stereocilia frequency curve (black dashed line) for units with different characteristic frequencies . A) Estimated neural tuning curves for high characteristic-frequency auditory fibers. B) Zoomed in on the low-frequency tails of the tuning curves in A). C) Estimated neural tuning curves for low characteristic-frequency auditory fibers

well as the nonlinear relationship between Ca^{2+} current and excytosis rate make it difficult to derive a quantitative relationship between CF, f_c and P. Additionally, as we shall see later on, the lack of a precise knowledge of the mechanical drive to the IHC stereocilia inhibits any meaningful quantitative approach in the estimation of the effect of transduction on the shape of neural tuning curves in low-CF regions. Due to these difficulties here we *qualitatively* illustrate the effect of transduction on the shape of neural tuning curves, and employ f_c = 500 Hz and P = 6 dB for all CFs.

RESULTS

To illustrate the effect of transduction on neural tuning curves, we draw hypothetical stereocilia frequency-tuning curves (black dashed-line in Fig. 2A) and from those we derive the corresponding neural tuning curves, by using the modelling results presented above. In particular the hypothetical stereocilia frequency-tuning curves are based upon frequency-tuning curves of high-CF AFs from Fig.7C of [13], and are identical when the frequency axis is expressed in octaves normalized to CF. In this manner we show the predicted qualitative differences between the frequency-tuning of the stereocilia and that of the AFs.

High-frequency units. The transduction process introduces differences between the frequency-tuning of the IHC stereocilia and that of the AF for frequencies well-below 4 kHz. For units with a CF larger than 4 kHz the distortions introduced by the transduction process affect the low-frequency tails of the tuning curve. Based on the assumption that mechanical responses to tones well-below CF grow approximately linearly with sound pressure, the neural tuning curves can be determined by subtracting Eq. (1) from the stereocilia frequency-tuning curve (black dashed line in Fig. 2A).

Figure 2A shows simulated neural tuning curves for units with different CF (indicated in legend), along with the stereocilia tuning curve (black dashed line). This figure shows that the transduction process introduces overall small differences between the tuning of the stereocilia and that of the AFs in the mammalian base. As expected, the differences between neural and mechanical tuning are observable in the low-frequency tails of the tuning curves (magnified in Fig. 2B). The transduction causes the tails of the neural tuning curves to (i) diverge from the stereocilia tuning curve as the frequency decreases, and (ii) to lie below the tail of the stereocilia tuning curve. The differences between the shape of stereocilia and AF tuning curves are qualitatively similar to those between BM-velocity and AF tuning curves recorded in the chinchilla base [9], though of a smaller magnitude.

Low-frequency units. For units with CF between about 1 and 4 kHz, the synaptic frequency sensitivity affects the relationship between stereocilia and AF frequency-tuning also near the tip of the tuning curves. Because in the tip

region the mechanical responses of the cochlea grow non-linearly with the sound pressure, it is not possible to derive the AF tuning curves by just linearly subtracting S (Eq. 1) from the stereocilia tuning curve. Rather, the compressive growth of the mechanical drive to the stereocilia needs to be accounted for. Because the precise mechanism deflecting the stereocilia is presently not known, and because the compressive growth of the mechanical responses varies with frequency and SPL, it is not possible to quantitatively establish the differences between AF and stereocilia frequency-tuning. However, assuming a growth of the mechanical drive to the stereocilia of 0.3 dB/dB allows to qualitatively visualize the effect of transduction on tuning curves for units with different CFs.

The resulting AF tuning curves are shown in Fig. 2C, along with the stereocilia tuning curve (black dashed line). This figure shows a broadening of the tip of the neural tuning curve relative to mechanical tuning when CF decreases from 4 to 1 kHz.

For CF<1 kHz the model does not predict particular differences between the tuning of the stereocilia and that of the AFs (data not shown). For units with a very low CF, the employed model might not be adequate, as harmonic distortions present in the mechanical drive to the cilia might introduce additional driving-frequency dependencies not captured with this simplified approach.

DISCUSSION AND CONCLUSIONS

Implications for cochlear mechanics. Comparisons of AF and BM tuning curves in the chinchilla base [9, 13] show that near the tip of the tuning curve, AF tuning resembles constant BM-velocity and BM-displacement contours. Well below CF, AF tuning curves lie between constant BM-displacement and constant BM-velocity contours. Overall, AF tuning is better fitted by constant BM-velocity contours than by constant BM-displacement contours [13]. Accounting for the effect of transduction, we conclude that in the chinchilla base the frequency-tuning of the IHC stereocilia is very similar to that of BM-velocity: the discrepancies between BM-velocity and AF tuning curves at low-frequencies can be explained, at least partially, by the transduction process.

In the classical view, because the IHC stereocilia are free-standing in the subtectorial space, their deflection reflects a high-pass filtered version of BM-displacement, i.e. the IHC stereocilia can be considered velocity detectors at low-frequencies and displacement detectors at high-frequencies. Our results, on the other hand, point out that in the chinchilla base the IHC stereocilia act as velocity detectors also at high-frequencies, up to CF. Furthermore, as the transduction machinery is similar across species, this result might apply to all species where the relationship between AF and BM is similar to that in the chinchilla (e.g. the guinea pig, see Fig.10 of [11]).

The lack of a strong "low-pass" relationship between BM-velocity and stereocilia tuning in the mammalian base bears several implications. First it contradicts explanations of the phase relationship between BM and IHC responses relying on the idea that the IHC stereocilia are driven by a high-pass filter version of BM-displacement (equivalent to a low-pass version of BM-velocity) with a cut-off frequency much smaller than CF [2]. We therefore propose that the relationship between BM and stereocilia vibrations might not be captured by a simple minimum-phase system as a linear filter; a non minimum-phase relationship between BM and stereocilia vibrations might be caused by different modes of vibration of the organ of Corti driving the stereocilia at high and low-frequencies.

Second, the apparent "BM-velocity detection" performed by the IHCs at high-frequencies might help to understand how the vibrations of the organ of Corti couple with those of the stereocilia. For example, by assuming that at high-frequencies the radial shear motion between the tectorial membrane (TM) and the reticular lamina (RL) induces a ciliary deflection proportional to the TM-RL radial shear displacement [3] would lead to conclude that either the TM-RL radial shear displacement approximates a 6 dB/octave high-pass filtered version of BM-displacement, or that a different mechanical drive is responsible for the ciliary deflection at high-frequencies. On the other hand, a compression of the RL-TM gap proportional to BM-displacement would produce a fluid-flow in the subtectorial space proportional to BM-velocity, providing a simple and plausible explanation for the inferred relationship between stereocilia and BM frequency-tuning at high-frequencies.

Implications for the CF-dependent mechanical frequency-tuning. It has been demonstrated in many different mammalian species that the AFs are more sharply tuned in the base than in the apex of the cochlea. In particular, the quality factor (Q) of the AF tuning curves systemically decreases with decreasing CF. The large differences between the Q of AF tuning curves in the base and in the apex implies that the Qs of the stereocilia tuning curves are different in the base and apex. Additionally a similar CF-dependence of Q for AF and BM tuning curves has been inferred from otoacoustic emission recordings [12]. Nonetheless, our results point out that the IHC-mediated transduction introduces a CF-dependent relationship between the Qs of AF and mechanical tuning curves.

Focusing the discussion on the chinchilla cochlea, nearly identical shapes of AF tuning curves were reported for CFs>4 kHz; for CFs between 4 and 1 kHz the tuning curves change in shape, getting progressively broader [13]. Lastly, for CFs below about 1 kHz, there is a second transition in the shape of the AF tuning curves, where the bandwidth of the tuning curves becomes larger for frequencies above than below CF [13]. Here we have shown that the transduction process produces a broadening of the neural (relative to mechanical) tuning curves for a decreasing CF between 4 and 1 kHz (Fig. 2C), thus contributing to the first transition in the shape of AF tuning curves. Based on our results, we exclude that this transition is caused entirely by the IHC-mediated transduction process. In fact, the data by [13] show that the broadening of neural tuning curves happens above and below CF, while our predictions in Fig. 2C show that the transduction process produces a broadening of the neural tuning curves only below CF. Nonetheless, our results suggest that the Q of the stereocilia tuning curves varies more slowly across CF than that of the AF tuning curves for CF>1 kHz, implying that the transition between basal "sharply-tuned" and apical "broadly-tuned" mechanics might be somewhat more abrupt than what appears from neural tuning curves.

Implications for cochlear models. The results presented here have two important consequences for cochlear mechanics models and their employment to predict the excitation of the IHC stereocilia. First, models of the cochlear micro-mechanics predicting a significantly sharper or shallower tuning of the IHC stereocilia relative to BM-velocity are unjustified in the light of this study. Second, models of the cochlear macro-mechanics (i.e. models of the BM motion) might be employed to drive models of transduction in order to predict realistic AF tuning curves by imposing a proportionality between stereocilia deflection and BM-velocity up to CF: the employment of BM-displacement or a low-pass filtered version of BM-velocity to drive the IHC stereocilia does not realistically capture the relationship between BM and AF tuning curves in the mammalian base.

To conclude, the present study points out that the IHC mediated transduction creates differences between the tuning of the stereocilia and that of the AFs. Such differences must be taken into account in order to understand the mechanical drive to the IHC stereocilia, e.g. when comparing optical-coherence tomography recordings of the organ of Corti motion with recordings from the auditory nerve.

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COMMENTS & QUESTIONS

[*Online Forum*]

Alberto Recio-Spinoso:

1. First line in the Results section: "...we employ a simple model of the frequency tuning of the stereocilia." To the occasional reader it is not clear how you arrived to the dashed lines in Fig. 2. Please elaborate.
2. The high-frequency slopes (i.e., above CF) of the tuning curves in Fig. 2C do not appear to change with CF, unlike the results in Fig. 7B in Temchin et al. 2008. Could you comment on that?
3. First three lines of Discussion and Conclusions: I think the data in the papers you make reference (ref. 9 and 13) show that near the tip of the tuning curve, AF tuning resembles both isovelocity and isodisplacement BM tuning curves. The overall shape is probably better fitted by constant velocity criteria, as mentioned by the authors.
4. Have you tried modeling two-tone rate suppression by low-frequency suppressors?

Author (A. Altoè): Dear Alberto, thank you for reviewing this paper. We modified the manuscript to include your comments 1-3. About comment 4, we did not model two-tone rate suppression but it is a very good idea and we will do so in our following studies.

Dáibhid Ó Maoiléidigh: Do you use the same parameter values throughout the entire cochlea? For all frequency ranges are all parameters the same?

Author (A. Altoè): Yes, we employed a model of a basal IHC and let the parameters be independent on the CF because in the mammalian base the electrical properties of the IHC do not seem to vary with CF. Differences between basal and apical IHCs have been reported (see ref. 6), mostly in the expression of the potassium channels. We did not account for these differences as they would hardly affect qualitatively the results presented here.

Christopher Bergevin: The synaptic strengths and other properties might vary randomly across synapses. Is this "static" stochastic nature of synapses accounted for in the study?

Author (A. Altoè): In ref. 1 we did so by randomizing the parameters of the synaptic transfer function (i.e., the function relating the whole-cell Ca^{2+} current with the release rate of neurotransmitter in the synaptic cleft). Although we did not explicitly mention the stochastic nature of the synapses (we discussed specifically the heterogeneity of Ca^{2+} signaling across synapses), we concluded that it creates a substantial variability in the value of P in Eq. (1) across different AFs. This variability is one of the factors preventing from precisely relate neural and mechanical tuning in the mammalian cochlea.
On the other hand, from a qualitative point of view, the frequency sensitivity of the AF is well described by Eq. (1) regardless of the parameters of the synaptic transfer function. Here we used a constant value of P because we wanted to discuss the qualitative differences between the frequency tuning of the stereocilia and that of the auditory nerve.